EXHIBIT 11

Neurourology and Urodynamics 35:407–411 (2016)

Clinical and Ultrasonographic Study of Patients Presenting with Transvaginal Mesh Complications

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Aim: The objective of this study was to investigate the clinical and ultrasonographic findings of women who had three-dimensional endovaginal ultrasound (EVUS) for the management of vaginal mesh complications. **Methods:** This was a retrospective study of patients that had EVUS due to mesh complications at a tertiary care center. The clinical charts were reviewed. The stored 3D volumes were reviewed regarding mesh information by two examiners independently. The predictive value of physical examination for detection of vaginal mesh was calculated. Patient outcomes were reviewed. **Results:** Seventy-nine patients presented to our center because of their, or their physicians' concern regarding mesh complications. Forty-one (51.9%) had vaginal/pelvic pain, and 51/62 (82.2%) of sexually active women experienced dyspareunia. According to ultrasonographic findings, mesh or sling was not demonstrated in six patients who believed they have had mesh/sling implantation. The positive predictive value for vaginal examination was 94.5% (95% CI: 84.9% 98.8%), negative predictive value was 12.5% (95% CI: 2.8% 32.4%), sensitivity was 72.2% (95% CI: 59.4% 81.2%), and specificity was 50.0% (95% CI: 12.4% 87.6%). Fifty-four patients were indicated for surgical treatment. Median postoperative review was 12 (range, 3 18) months and 38/53 (71.7%) patients were satisfied. **Conclusions:** The most common complaints of vaginal mesh complications were pain and dyspareunia. EVUS appeared to be helpful for assessing mesh presence, location, and extent including planning for surgical intervention. *Neurourol. Urodynam. 35:407 411, 2016.* © 2015 Wiley Periodicals, Inc.

Key words: complications; prolapse; transvaginal mesh; ultrasonography; urinary incontinence

INTRODUCTION

Over the last 10 years transvaginal mesh (TVM) repair for pelvic organ prolapse POP has been used increasingly with encouraging anatomical short-term results.[1] The anterior or posterior meshes are placed in order to provide a strong, durable support of the bladder or the rectum. The mesh implants have a configuration designed to extend from the bladder neck in the vesicovaginal space when used for support of the anterior vaginal wall, or from the perineum to the vaginal apex, occupying the rectovaginal space, when used for posterior repair. The midurethral sling (MUS) was developed to supplement midurethral function in women with stress urinary incontinence by allowing the ingrowth of new host tissue.[2]

The placement of mesh increased rapidly in POP and stress incontinence surgery; however, many complications occurred due to inappropriate techniques, and many complications were recognized too late and were poorly managed. In 2011, the United States Food and Drug Administration issued an updated safety communication stating that serious complications associated with transvaginal mesh for POP repair are not rare. Complications unique to mesh (vaginal mesh extrusion, urinary tract erosion, and mesh contraction)are being reported with increasing frequency.[3] Some of these complications are new and unique and require innovative surgeries that may or may not correct the problem. Symptoms of suspected vaginal mesh complications include vaginal discharge and/or bleeding, dyspareunia, pelvic pain, and recurrent urinary tract infections

Ultrasound imaging appears to be helpful for assessing transvaginal mesh and midurethral slings because they both consist of similar material and the theoretical concept of tension-free stabilization is the same for both approaches. Moreover, both polypropylene vaginal meshes and polypropylene suburethral slings are hyperechogenic.[4] Previous studies have reported the feasibility of evaluating meshes by standardized two-dimensional (2D), three-dimensional (3D), and four-dimensional (4D) ultrasonography using translabial, introital and endovaginal approaches.[5 9]

Regarding mesh complication detection, in the absence of operative reports, the evaluating physician has to resort to assessment by palpation in a standard fashion. No validation has been performed for the clinical examination. The objectives of this study were: (i) to investigate clinical and ultrasonographic findings of women who had three-dimensional endovaginal ultrasound for the management of vaginal mesh complications after prolapse repair and midurethral sling; (ii) to determine the sensitivity and specificity of physical examination compared to ultrasonographic findings for mesh complications; and (iii) to study the relationship between the ultrasonographic position of midurethral slings and voiding dysfunction.

MATERIALS AND METHODS

This was a retrospective study of patients that had three-dimensional endovaginal ultrasound (EVUS) and/or translabial

Eric Rovner led the peer review process as the Associate Editor responsible for the paper.

Potential conflicts of interest: Nothing to disclose.

Authors Participation: Manonai J: Data collection, data analysis, manuscript writing. Rostaminia G: Data collection, manuscript editing. Denson L: Graphics, manuscript editing. Shobeiri SA: Project development, manuscript editing.

Grant sponsor: Dr. Jittima Manonai has received an ICS research grant.

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Received 21 September 2014; Accepted 24 November 2014

Published online 25 January 2015 in Wiley Online Library (wileyonlinelibrary.com).

DOI 10.1002/nau.22725

ultrasound due to mesh complications from July 2010 to December 20012 at a tertiary care center. This study was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center. Clinical charts were reviewed to obtain the presenting symptoms, medical and surgical history, examination findings, surgical intervention, and outcome results. Postoperative outcome was defined as patient satisfaction. Exclusion criteria were incomplete charts and poor ultrasound image quality. The definitions used in the study conform to the IUGA/ICS terminology for pelvic floor dysfunction.[10]

The methodology for performing multicompartmental pelvic floor sonography has been reported previously.[11] Mesh was identified as the hyperechogenic structure. The honeycomb-like appearance can distinguish mesh from scar or autologous fascial slings. Two examiners independently reviewed the stored 2D/3D volumes of the selected patients. The senior author, SAS, reviewed the findings in which there were disagreements between the two readers (JM and GR). The following were assessed.

- Mesh/sling number and location
- Distance between the lower margin of the anterior mesh and the urethral meatus
- Distance between the lower margin of the posterior mesh and the perineal body
- Distance of sling from the vesicourethral junction in 48/73 (65.7%) patients. Tape position along the urethra was measured and expressed as a percentage of the urethral length refered to as "tape percentile," as follows: proximal urethral length (distance from vesicourethral junction to mid-point of tape) divided by total urethral length (distance from vesicourethral junction to external urethral meatus) in the sagittal plane, with the vesicourethral junction and the external urethral meatus representing 0% and 100% of the urethral length (i.e., 0th and 100th percentile), respectively.[12]

Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC). Summary statistics were calculated for the patient population. Sensitivities and specificities for physical examination compared to ultrasonography were calculated. Chi-square test was used to determine whether there was a significant difference between each tape percentiles in severity of incontinence symptom. Appropriate parametric or nonparametric tests were used to analyze continuous variables. A *P*-value of less than 0.05 was considered significant for all analyses.

RESULTS

A total of 87 patients were identified. All of them presented to our center because of their or their physicians' concern regarding mesh complications. Patients with non-vaginal mesh (n 1), non-mesh related problems (n 3), and incomplete charts (n 4) were excluded from the study. The final analyses included 79 patients. The mean age was 56.1 ± 12.2 years and the mean body mass index was $29.6 \pm 6.4\,kg/m^2$. Regarding previous surgical procedures, 77.2%, 60.7%, and 41.8% had hysterectomy, prolapse repair and surgery for stress urinary incontinence, respectively.

All patients underwent the initial mesh repair for pelvic organ prolapse and/or midurethral sling for stress urinary incontinence in different institutions and were referred to our tertiary referral center for the management of mesh complications. Thirteen out of seventy-nine (16.4%) patients underwent mesh excision/revision between the mesh implantation and presenting to our unit.

The presenting symptoms and examination findings are detailed in Table I and demonstrate that 41/79 (51.9%) patients had vaginal and/or pelvic pain, which was aggravated by movement, and 51/62 (82.2%) of sexually active women experienced dyspareunia.

The 2D/3D ultrasonographic findings of 73 patients are demonstrated in Table II. Mesh or sling was not demonstrated in six patients who believed they have had mesh/sling implantation. As a result, 73/79 (92.4%) did have mesh on ultrasound. Forty-four out of forty-eight (91.7%) patients and 4/48 (8.3%) patients had one and two midurethral slings in place, respectively. Regarding the sling location, the tape percentile was used as an indication of sling position along the urethra with respect to urethral length (Table II). Nine out of sixteen (56.2%) of patients with sling location under the proximal urethra (<40 percentile) reported that they were moderately or greatly bothered by urine leakage related to physical activity using the Urinary Distress Inventory Questionnaire (UDI 6). While 12/32 (37.5%) of patients with sling location under the midurethra (40–70 percentile) or the distal urethra (>70 percentile) reported equally bothersome symptoms. There was no significant difference between both groups (*P* 0.217).

On vaginal examination, 55/79 (69.6%) patients had prominent tense focal areas of mesh palpated under the vaginal epithelium and palpation of those areas reproduced the pain they experienced with movement and/or sexual intercourse. The pelvic examination was positive for mesh in 52/73 (72.2%) patients with vaginal mesh. It was negative in three out of six (50%) patients without vaginal mesh. As a result, the positive predictive value was 94.5% (95% CI: 84.9%–98.8%), negative predictive value was 12.5% (95% CI: 2.8%–32.4%), sensitivity was 72.2% (95% CI: 59.4%–81.2%), and specificity was 50.0% (95% CI: 12.4%–87.6%) using ultrasound as the gold standard. The accuracy of vaginal palpation for mesh detection in patients with mesh-related complaints was 69.6%. Figure 1 demonstrates a remaining piece of midurethral sling in the anterior vaginal wall, which could not be palpated on pelvic examination.

Fifty-four patients were indicated for surgical treatment, one refused due to personal reasons. The details of surgical interventions are shown in Table III. The most common indication for surgery was mesh exposure (81.1%). One patient had her intravesical sling removal transvaginally and the

TABLE I. Presenting Symptoms and Physical Findings (N = 79)

	n (%)
Symptoms	
Pain	41 (51.9%)
Discharge	6 (7.6%)
Bleeding	11 (13.9%)
Bulge	14 (17.7%)
Urinary symptoms	11 (13.9%)
Unknown	2 (2.5%)
POP Q examination	
Genital hiatus (cm); median (range)	3 (1 6)
Perineal body (cm); median (range)	3 (2 5)
Total vaginal length (cm); median (range)	8 (2 12)
Pelvic examination	
mesh palpable under vaginal epithelium	55 (69.6)
mesh seen/palpable above vaginal epithelium	42 (53.2)

TABLE II. Ultrasonographic Findings (N = 73)

Findings	
Midurethral sling (N = 48), number (percent)	
Tape percentile	
0 < 40	16 (33.3%)
40 70	29 (60.4%)
> 70	3 (6.3%)
Anterior mesh (N = 20), mean (SD)	
1. Length (mm)	24.1 (9.9)
2. Distance between the lower margin and the urethral meatus (mm)	22.5 (6.7)
Posterior mesh (N = 26), mean (SD)	
1. Length (mm)	32.5 (10.2)
2. Distance between the lower margin and the perineal body (mm)	9.7 (7.0)

TABLE III. Details of Surgical Interventions

	n (%)
Indications for surgery (n = 53)	
mesh exposure	43 (81.1%)
mesh with pain	5 (9.4%)
tight sling/improper position	3 (5.7%)
scar	1 (1.9%)
bladder erosion	1 (1.9%)
Procedures (n = 53)	
mesh excision/revision/ removal only	43 (81.1%)
mesh excision/revision/ removal + prolapse repair	10 (18.9%)
Complications (n = 4)	
urethral injuries	2 (3.8%)
vaginal epithelial necrosis	1 (1.9%)
hematoma	1 (1.9%)

ultrasonographic finding was demonstrated in Figure 2. Prolapse repair was a concomitant procedure in 10 (18.9%) patients. Mesh removal under ultrasound guidance was performed in three (4.0%) patients. Two cases (3.8%) of urethral injury were found and urethral repair was performed without immediate and long-term complications. One case of surgical site hematoma and one case of vaginal epithelial necrosis were presented due to the extensive removal of mesh. However, they were treated conservatively without other complications.

Regarding the outcome after surgical intervention, median (range) postoperative review was 12 (3–18) months and 38/53 (71.7%) patients were satisfied. Four (7.5%) patients experienced bothersome stress urinary incontinence after their midurethral slings were removed, three had urethral bulking agent injections and the other had a pubovaginal sling operation. One (2.0%) patient had native tissue repair because of anterior and posterior wall prolapse. One (2.0%) patient had repeated mesh excision procedure because of her intractable pain; her pelvic and vaginal pain resolved after the second surgery. Ten patients (19.0%) had the same or worsened pelvic/vaginal pain and/or dyspareunia postoperatively.

DISCUSSION

The goal of this study was to investigate the clinical and ultrasonographic findings of women who had three-dimensional endovaginal ultrasound for the management of vaginal mesh complications after prolapse repair and midurethral sling. In addition, this study endeavored to determine whether vaginal examination findings and/or a cluster of patient history were accurate for diagnosis of vaginal mesh complications, when compared against 2D/3D ultrasonographic findings. Vaginal mesh exposure, contraction and other complications can be serious and are associated with substantial morbidity. They may result in pelvic/vaginal pain on movement and dyspareunia. In addition, delay in diagnosis can cause chronic problems, which are difficult to treat even after the removal of the mesh. Our findings also suggest that absence of vaginal mesh in patients with previous vaginal operations cannot be excluded based on physical examinations alone. To our knowledge, this is the first clinical study involving a cohort of patients in a situation of diagnostic uncertainty that actually investigated vaginal mesh complications.

Vaginal mesh surgery for pelvic organ prolapse and stress urinary incontinence is a relatively new technique, involving a new set of complications that has to be learned by the surgeons inserting mesh and by the practitioners that are likely to deal with the women receiving the mesh. It has been shown that the majority of patients self-refer to another physician after mesh complication.[13] This coupled with the fact that operative reports are generally not available, leaves the evaluator at the mercy of clinical intake and physical examination to make a sound clinical judgement. Evaluation of mesh complication is performed by digital palpation and by translabial, introital or endovaginal ultrasound.[5 9] Generally, diagnosis of mesh exposure is simple because it may be

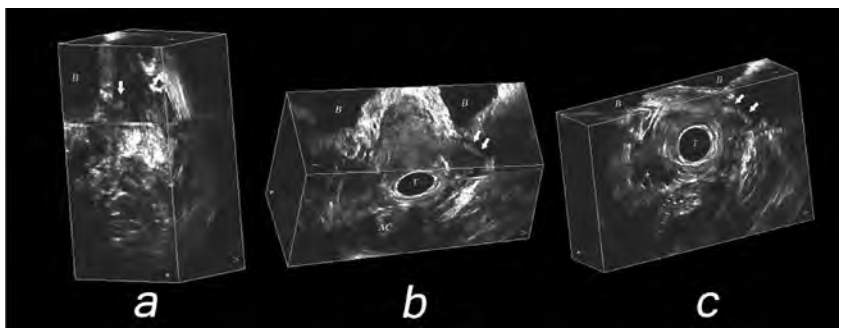

Fig. 1. The sagittal (a), coronal (b), and axial (c) views of three dimensional ultrasound volume demonstrating a piece of sling (arrows). B indicates bladder; T, transducer; and AC, anal canal.

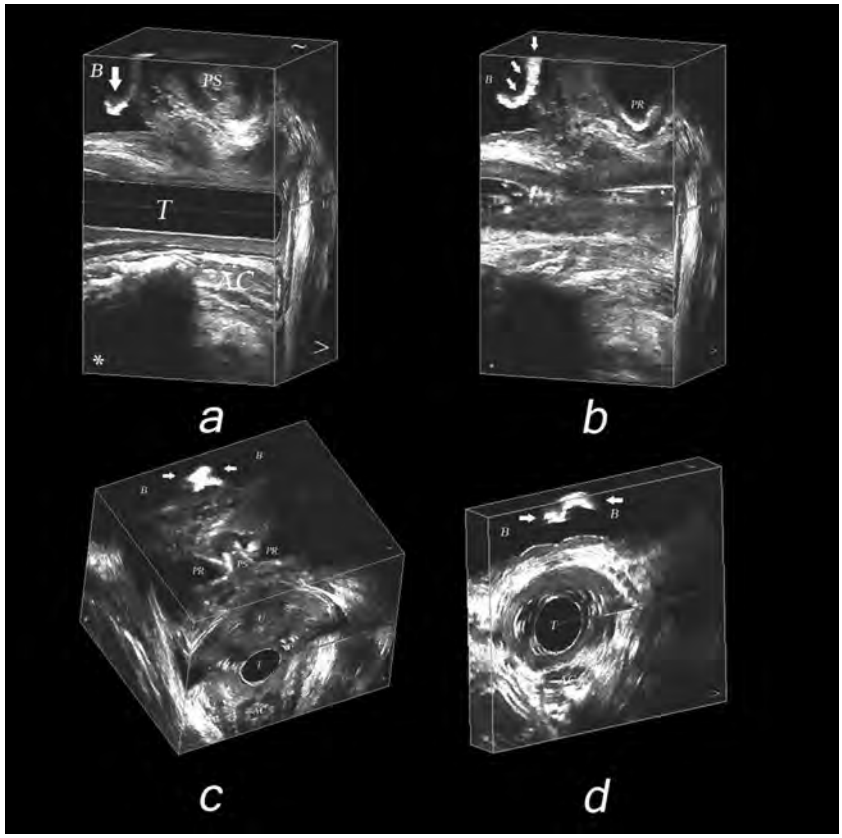

Fig. 2. The sagittal (a and b), coronal (c), and axial (d) views of three dimensional ultrasound volume demonstrating a sling in the bladder (arrows). B indicates bladder; T, transducer; AC, anal canal; PS, pubic symphysis; and PR, pubic rami.

clinically obvious. Vaginal mesh contraction is a serious complication after pelvic organ prolapse repair using polypropylene mesh. It is characterized by severe vaginal pain and dyspareunia and on vaginal examination localized areas of tense and tender tissue.[14] However, uncertainty about surgical history, a short and narrow vaginal caliber, and vaginal scarring may affect the level of confidence that clinicians feel about their diagnosis. Hence, it may be useful to determine the number, location, and type and extent of the sling and/or mesh using ultrasound especially in patients who do not remember or do not know the exact nature of their surgery.[15] In this study, the ultrasonographic findings not only aided in planning for surgical interventions in cases of bladder erosion, misplaced or tight midurethral slings, associated vaginal wall defects, but also guided mesh location during mesh excision procedure.

The present study showed that vaginal examinations have a high positive predictive value and an acceptable sensitivity for detection of vaginal mesh. However, as a screening modality for evaluation of mesh complications, a negative result from vaginal examination was not an acceptable modality for reassuring a patient that they did not have the mesh/sling (NPV 12.5%) and only correctly identified 50.0% of those who did not have the mesh/sling. Based on these findings, we support the use of ultrasound evaluation in referral settings in which the patient's surgical history of meshes is uncertain and a decision needs to be made on whether surgical intervention is necessary.

Persistent pain after mesh implantation is a serious matter. It may be the consequence of nerve entrapment or mesh contraction. Surgical intervention is often required to alleviate symptoms. It basically involves mobilization of the mesh, division of the fixation arms, and excision of contracted mesh. Apart from possible irreversible damage to the nerve in the case of nerve injury, secondary vaginismus may occur. Secondary vaginismus is caused by the woman's fear of the pain and is quite difficult to treat.[16]

This study is not without limitations. Firstly, it is a retrospective study and retrospective analysis has been identified as a potential for bias. Secondly, our data are from the referral setting and our physical examination skill or surgical technique may also have played a significant role in the results of the present study. Thirdly, one important limitation of transvaginal or translabial ultrasound is that it cannot detect mesh that is located outside the vagina, such as the arms of midurethral slings. These limitations may be resolved in future studies focusing on the multicenter, prospective collection of data. Using ultrasound, the dimensions of the mesh can be assessed postoperatively and compared with those of the original mesh to define mesh contraction or shrinkage. Additionally, imaging may be useful to determine the biomechanical association between mesh and symptoms because mesh complications may be encountered more frequently in the future.

CONCLUSIONS

The most common vaginal mesh and/or midurethral sling complications are pain and dyspareunia. Three-dimensional endovaginal ultrasound (EVUS) appears to be helpful for assessing

mesh presence, location, and extent allowing planning for suitable and comprehensive surgical intervention.

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